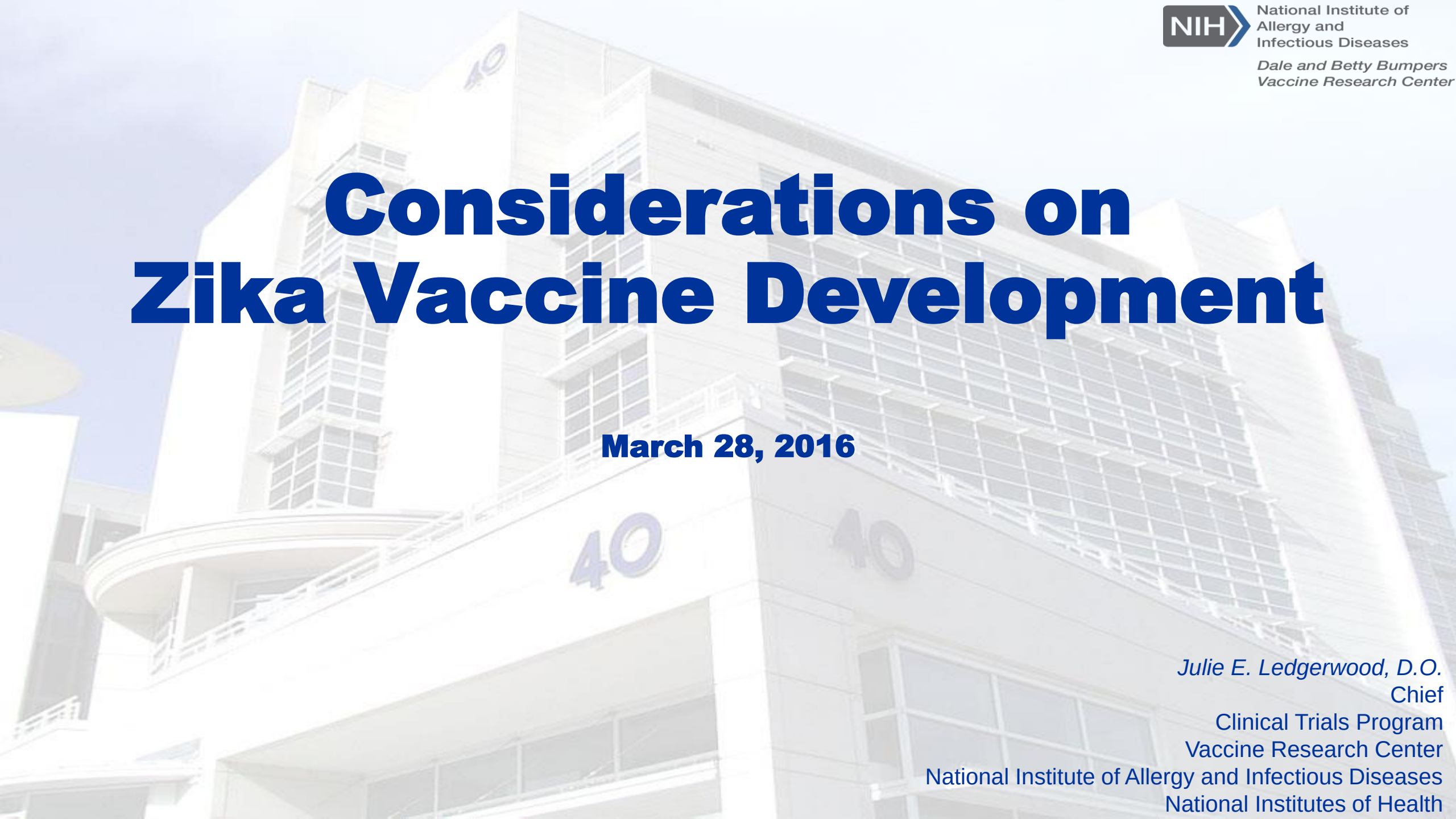

National Institute of Allergy and Infectious Diseases
Dale and Betty Bumpers Vaccine Research Center

Considerations on Zika Vaccine Development

March 28, 2016

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Vaccination for Congenital Infections: Lessons from Rubella

- Congenital Rubella Syndrome (CRS): Infants born with blindness, deafness, heart defects, often microcephaly
- Between 1964-1965, 50,000 pregnant women in U.S. exposed to Rubella
  - 20,000 infants born with CRS
- With MMR vaccine administered to general population, CRS has all but disappeared

National Library of Medicine

Zika Vaccine Target Population

- Initially women of childbearing age
  - Target population at greatest risk

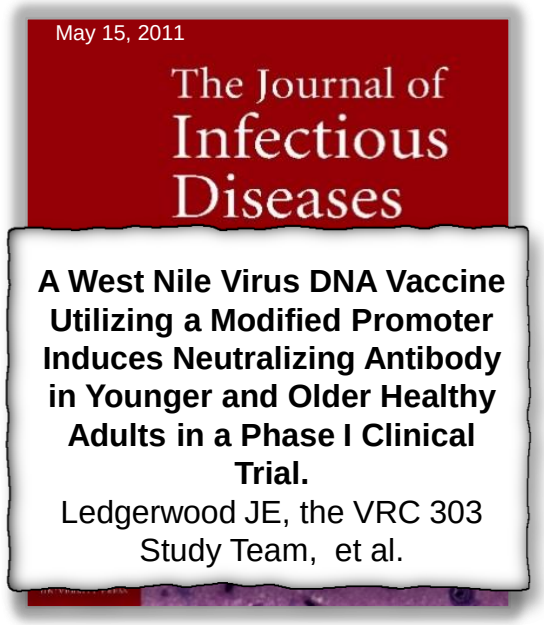
- General population
  - Herd immunity
  - Protect pregnant women and developing fetus
  - Rubella vaccination model

Flavivirus Vaccines

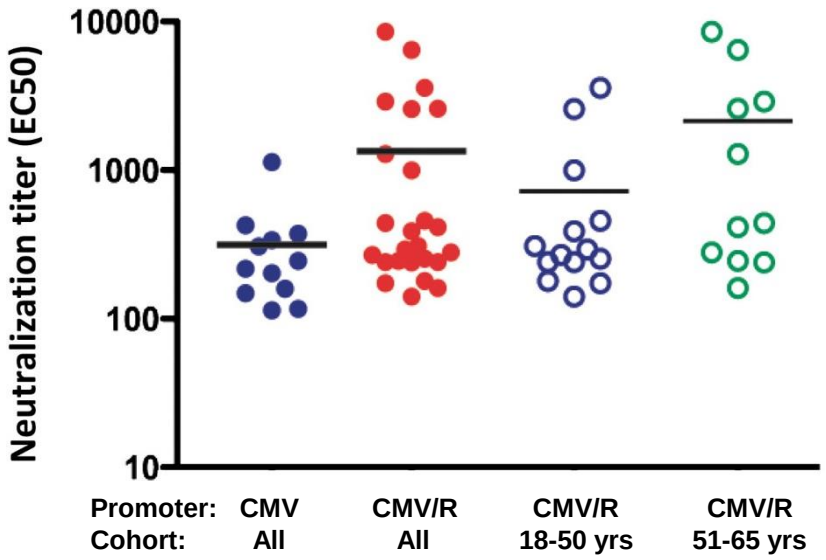
- **Yellow Fever Vaccine**
  - Effective against 7 genotypes
  - Protective titer ≥1:10
  - High efficacy rates
- **JEV and TBE* Vaccines**
  - Protective titer ≥1:10
  - High efficacy rates
- **Investigational Dengue and WNV vaccines**
  - Multiple platforms have been tested
  - E protein induced neutralizing antibody
- **Protective immune response to vaccination (E protein)**
  - Neutralizing Antibody
  - Structural considerations for antigen design

*not licensed for use in US

West Nile Virus VRC DNA Vaccine



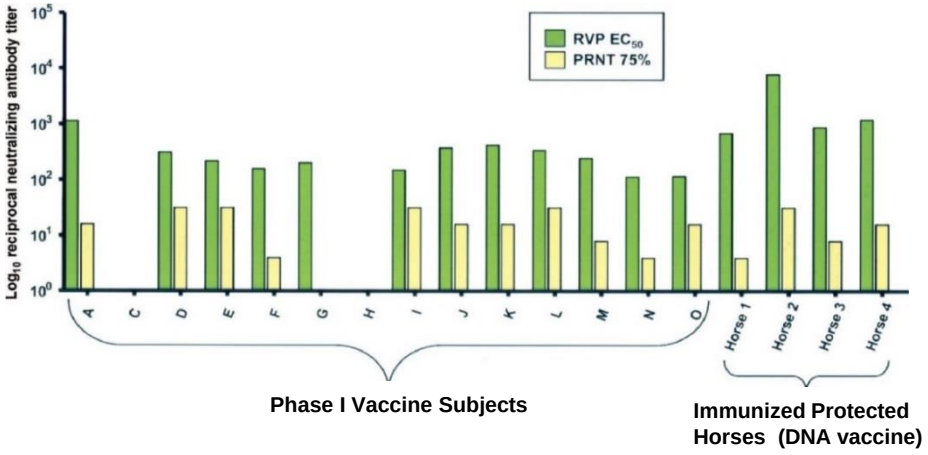
NAb (EC50) by RVP neutralization assay responses at week 12 (4 weeks after 3rd vaccination)



Julie E. Ledgerwood et al. J Infect Dis. 2011;203:1396-1404

West Nile Virus
DNA Vaccine (Phase 1)

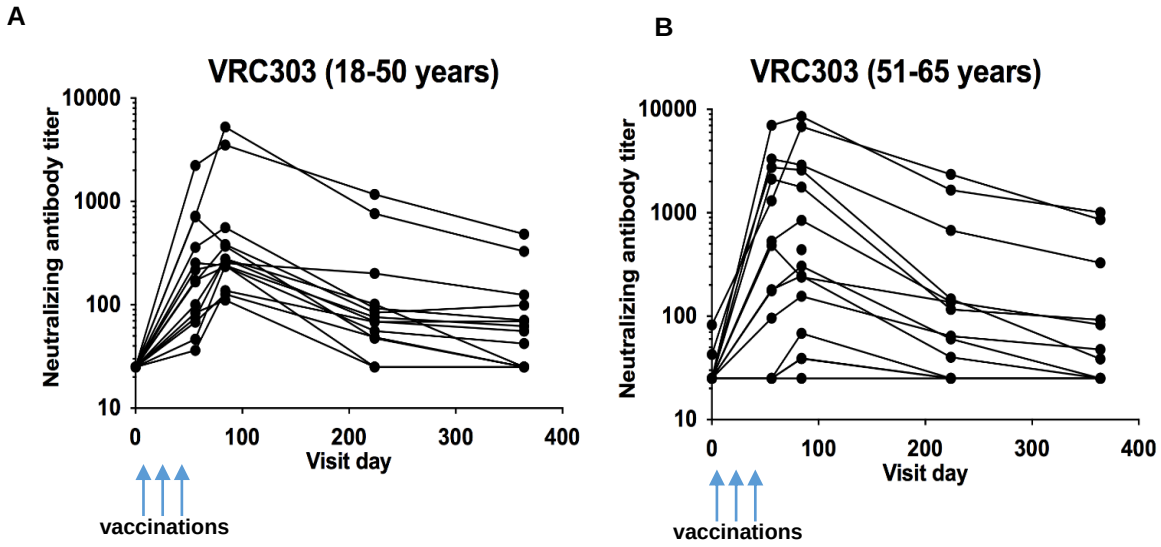
Phase I: Week 12 (4 weeks after 3rd vaccination)
Horses: 3 weeks after 1-mg dose WNV DNA vaccine



WNV reporter-virus particles (RVP) neutralization assay and plaque reduction neutralization (PRNT)

Martin et al. J Infect Dis. 2007;196:1732-1740

NAb was measured throughout the trial:
(A) 18–50-year-old (B) 51–65-year-old



Ledgerwood et al. J Infect Dis. 2011;203:1396-1404

Zika Vaccine Clinical Development

- Research and down-selection of platform and antigen design
  - Role of prior Flavivirus vaccine research
- Preclinical assessment
  - Animal models needed to study pathogenesis and evaluate efficacy
- Phase 1 safety and immunogenicity
  - Zika naïve
  - Flavivirus naïve vs general population
  - Endemic vs nonendemic regions
- Phase 2 safety and immunogenicity for regimen and dose
- Human challenge efficacy data
- Phase 2B
  - Efficacy endpoint/design options

Zika VRC DNA Vaccine: Phase 1 Study

Phase I, randomized, multicenter clinical trial to evaluate the safety and immunogenicity of a Zika DNA vaccine in healthy adults 18-60 years old.

VRC 319 Study Schedule						
Group	**Subjects**	**Day 0**	**Week 4**	**Week 8**	**Week 12**	**Week 20**
1	20	Zika DNA				
2	20	Zika DNA			Zika DNA	
3	20	Zika DNA	Zika DNA	Zika DNA		
4	20	Zika DNA	Zika DNA			Zika DNA
Total	80	*Zika DNA injections are 4 mg in 1 mL IM*				

Zika Vaccine Phase 2B Efficacy Trial Endpoint Options

- **Option A: Diagnosis by seroconversion**
  - Confounded by cross reactivity with Dengue, YF
  - Confounded by vaccine response to Env protein (PRNT or ELISA) and natural infection does not consistently induce responses to internal proteins
  - Is it possible to evaluate by T cell response to internal proteins

- **Option B: Diagnosis by PCR of symptomatic cases only**
  - Underestimates case count since 70%+ are subclinical or asymptomatic, and because of teratogenicity associated with asymptomatic infection, need to prevent all viremia

- **Option C: Diagnosis by frequent urine PCR *plus* investigation of symptomatic cases**
  - Advantages include more accurate case count and reduction of trial size
  - ***Need additional data: urine PCR sensitivity in asymptomatic cases***

Zika Vaccine Phase 2B Efficacy Trial Design Options

Assumptions:

- **Double-blind, placebo-controlled, 1:1 randomized trial**
- **5% Zika incidence in placebo group, 70% vaccine efficacy, 90% power**
- **25% of Zika infections result in symptoms prompting evaluation**

Option A (Seroconversion)

- **No clear path forward in a vaccine trial unless T cell response to antigens not contained in vaccine could substitute**

Option B (Plasma/Serum or Urine to Diagnose Symptomatic Cases Only)

- **2100 per group, n=4200 total**

Option C (Urine PCR 3x Month, Goal to Diagnose All Cases)

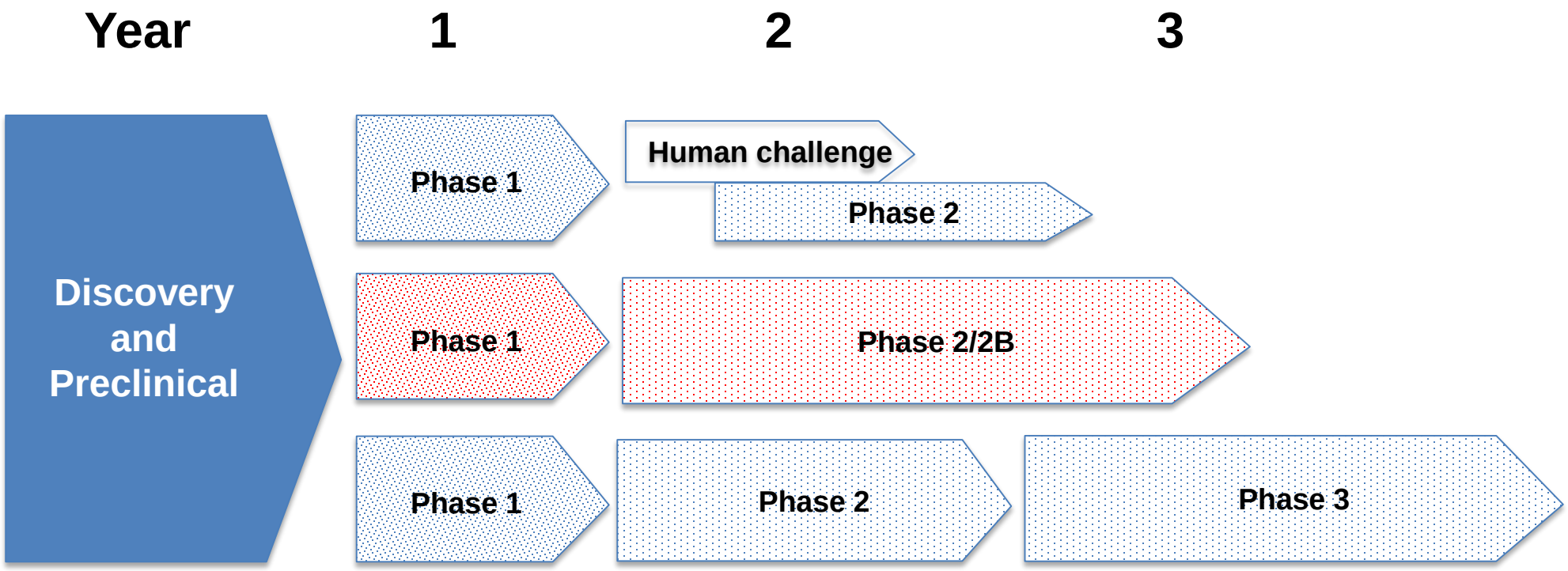
- **525 per group, n=1050 total**

*Trial size estimations include 20% overage to account for drop out

Zika Vaccine Efficacy Evaluation by Human Challenge

- **Human challenge with Dengue is well established**
- **Zika virus causes relatively mild symptoms in adults**
- **Advantages**
  - Demonstrate kinetics of virus clearance from all body compartments
  - Define clinical manifestations
  - Measure immune response patterns
  - Obtain clinical samples for reagents and generation of human mAbs
  - Evaluate diagnostics and efficacy of candidate vaccines and therapeutics
- **Concerns**
  - Guillain-Barre or other unexpected adverse events
  - Would need to avoid conception in women and sexual transmission by men
  - Direct challenge with needle and syringe may differ from mosquito transmission
- **Other considerations**
  - Could obtain efficacy data on prevention of viremia in small number of subjects
  - Would need to determine with regulatory authorities how this information would contribute to product development and licensure

Zika Vaccine Development Approaches

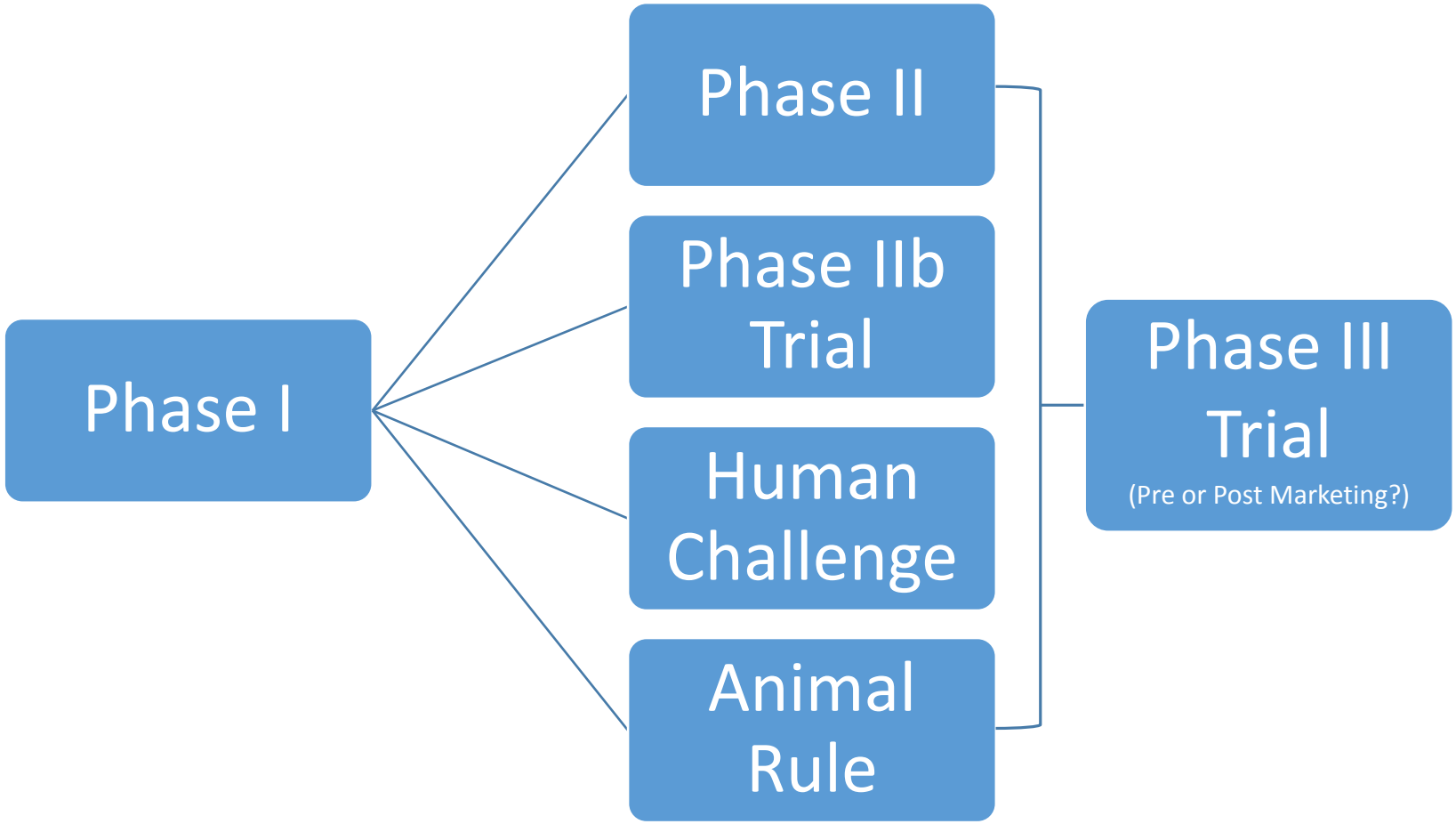


Summary

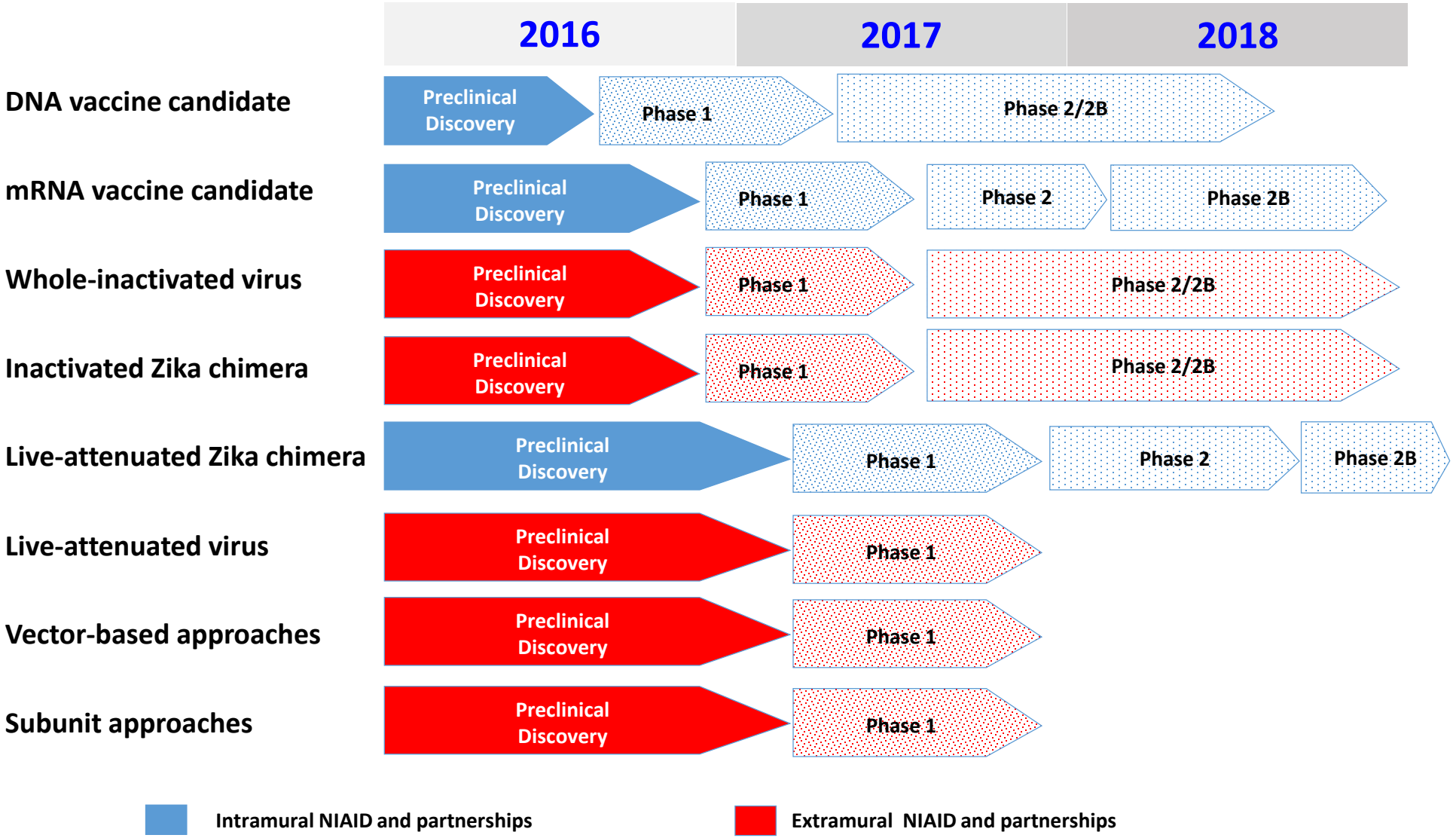
- Prior flavivirus immunology and vaccine research is informative
- Animal models for immunogenicity and efficacy are needed
  - Understanding disease and data for evaluation of candidates
- Ongoing epidemiology and human disease research will inform vaccine trials design and target populations
- Data from phase 1 and human challenge could guide down-selection
- Further considerations on timing and endpoints of Phase 2/2B and human challenge data to assess efficacy and support broad use

Extra slides

Zika Vaccine Clinical Development



Zika Vaccine
Proposed Development Timeline



NIAID Vaccine Research

- **Vaccine research – intramural candidates**
  - **DNA expressing preM and E (NIAID, VRC)**
  - **Live attenuated Dengue-Zika chimera (NIAID, LID)**

- **Vaccine research – extramural candidates (Academic and Industry collaborations)**
  - **Live attenuated or live chimeric virus**
  - **Whole inactivated virus or inactivated chimeric virus**
  - **mRNA platforms (SAM, others)**
  - **Replicating viral: VSV platform**
  - **Replication-defective Viral Vector: MVA**
  - **Subunit protein, VLP**

Special Populations: Pregnant Women

Vaccine	Before pregnancy	During pregnancy	After pregnancy	Type of Vaccine
Hepatitis A	Yes, if indicated	Yes, if indicated	Yes, if indicated	Inactivated
Hepatitis B	Yes, if indicated	Yes, if indicated	Yes, if indicated	Inactivated
Human Papillomavirus (HPV)	Yes, if indicated, through 26 years of age	No, under study	Yes, if indicated, through 26 years of age	Inactivated
Influenza IIV	Yes	Yes	Yes	Inactivated
Influenza LAIV	Yes, if less than 50 years of age and healthy; avoid conception for 4 weeks	No	Yes, if less than 50 years of age and healthy; avoid conception for 4 weeks	Live
MMR	Yes, if indicated, avoid conception for 4 weeks	No	Yes, if indicated, give immediately postpartum if susceptible to rubella	Live
Meningococcal: • polysaccharide • conjugate	If indicated	If indicated	If indicated	Inactivated Inactivated
Pneumococcal Polysaccharide	If indicated	If indicated	If indicated	Inactivated
Tdap	Yes, if indicated	Yes, vaccinate during each pregnancy ideally between 27 and 36 weeks of gestation	Yes, immediately postpartum, if not received previously	Toxoid/ inactivated
Tetanus/Diphtheria Td	Yes, if indicated	Yes, if indicated, Tdap preferred	Yes, if indicated	Toxoid
Varicella	Yes, if indicated, avoid conception for 4 weeks	No	Yes, if indicated, give immediately postpartum if susceptible	Live

CDC, 2016

Vaccines Administered During Pregnancy

- Hepatitis A (if indicated)
- Hepatitis B (if indicated)
- Influenza IIV
- Meningococcal (if indicated)
- Pneumococcal (if indicated)
- Tdap (ideal between 27 and 36 weeks of gestation)
- Tetanus/Diptheria Td (if indicated, Tdap preferred)

CDC, 2016

Phase 2/2B Potential Design

Schema			
Group	Subjects	Day 0	Week 12
Part 1 (Non-endemic for Safety and Immunogeniciy)			
1	1000	Zika vaccine	Zika vaccine
2	250	Placebo	Placebo
Part 2 (Endemic Population with Efficacy Endpoint)			
3	600	Zika vaccine	Zika vaccine
4	600	Placebo	Placebo
Total	2450		

WNV DNA Vaccine References

- **Neut RVP Assay:** A rapid and quantitative assay for measuring antibody-mediated neutralization of West Nile virusinfection. Pierson TC, Sánchez MD, Puffer BA, Ahmed AA, Geiss BJ, Valentine LE, Altamura LA, Diamond MS, Doms RW. Virology. 2006 Mar 1;346(1):53-65. Epub 2005 Dec 2.

- **Horse DNA Vaccine:** West Nile virus recombinant DNA vaccine protects mouse and horse from virus challenge and expresses in vitro a noninfectious recombinant antigen that can be used in enzyme-linked immunosorbent assays. Davis BS, Chang GJ, Cropp B, Roehrig JT, Martin DA, Mitchell CJ, Bowen R, Bunning ML. J Virol. 2001 May;75(9):4040-7.

- **VRC 302 – CMV Promoter:** A West Nile virus DNA vaccine induces neutralizing antibody in healthy adults during a phase 1 clinical trial. Martin JE, Pierson TC, Hubka S, Rucker S, Gordon IJ, Enama ME, Andrews CA, Xu Q, Davis BS, Nason M, Fay M, Koup RA, Roederer M, Bailer RT, Gomez PL, Mascola JR, Chang GJ, Nabel GJ, Graham BS. J Infect Dis. 2007 Dec 15;196(12):1732-40.

- **VRC 303 – CMV/R Promoter:** A West Nile virus DNA vaccine utilizing a modified promoter induces neutralizing antibody in younger and older healthy adults in a phase I clinical trial. Ledgerwood JE, Pierson TC, Hubka SA, Desai N, Rucker S, Gordon IJ, Enama ME, Nelson S, Nason M, Gu W, Bundrant N, Koup RA, Bailer RT, Mascola JR, Nabel GJ, Graham BS; VRC 303 Study Team. J Infect Dis. 2011 May 15;203(10):1396-404.